DEPARTMENT OF HEALTH AND HUMAN SERVICE

Food and Drug Administration
San Juan District
466 Fernandez Juncos Avenue
San Juan PR 00901-3223

Telephone: (787) 474-9500
FAX: (787) 729-6658

June 19, 2006

WARNING LETTER
SJN-06-10

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Dr. Allen Chao, PhD
Chairman and CEO
Watson Laboratories Caribe, Inc.
311 Bonnie Circle
PO Box 1900
Corona, CA 92878-1900

Dear Dr. Chao:

On November 3 through December 15, 2005, the Food and Drug Administration (FDA) conducted an inspection of your manufacturing facility in Humacao Industrial Park, Rd 3 Km 76.9 Humacao, Puerto Rico. The inspection revealed significant deviations from Current Good Manufacturing Practice (CGMP) regulations, Title 21 Code of Federal Regulations (CFR), Parts 210 and 211, in the manufacture of drug products. These CGMP deviations were listed on an Inspectional Observations (FDA-483) form issued to you at the close of the inspection. These CGMP deviations cause your drug products to be adulterated within the meaning of section 501(a) (2) (B) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 351(a) (2) (B)).

We also have completed review of your December 27, 2005 response to the FDA-483 observations. The CGMP violations discussed below have not been adequately addressed by your response. In addition, we are concerned with your decision to releasing four lots of drug product associated with an investigation that had not been completed. We acknowledge that on December 8, 2005, three days after the inspection ended, you decided to recall these four lots of product.

Examples of these deficiencies are included as follows:

1. Failure to handle and store components and drug product containers in a manner to prevent contamination. Your handling and identification of sieved materials is inadequate because they do not prevent the possibility of using an incorrect component or active ingredient in the manufacturing process of your drug products. **[21 CFR Part 211.80 (a)]**

   Specifically, your firm did not follow appropriate process controls during the manufacture of Clindamycin HCL capsules (an antibiotic), lots [redacted] and [redacted]. These lots were manufactured on [redacted] and [redacted], respectively. On August 2005, during the review of the assay data, an atypical peak was detected on both chromatographic runs.

Further investigation revealed that Trazodone HCl salt, the active ingredient in Trazodone HCl tablets (an anti-depressant), was erroneously identified as lactose and used during the manufacture of these lots of Clindamycin HCl capsules. Trazodone HCl salt and lactose were sieved and weighed the same day. Even though these two lots were rejected, other Clindamycin HCl lots manufactured under the same campaign, which met release specification test results were released (August 2005) to the market prior to the completion of the investigation (November 2005). All lots were manufactured in the same equipment and only minor cleaning was performed between lots. Your proposed corrective actions include providing more detailed instructions on procedures for handling and labeling raw materials in preparation for drug product manufacturing, developing a visual aid system to track the partial materials, and identifying a mechanism for documentation of the raw material drums. However, no examples or specifics were provided.

2. Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that in-process materials and drug products conform to appropriate standards of identity, strength, quality and purity. **[21 CFR Part 211.160(b)]**

Specifically, in February 2005 aberrant and out-of-specification (OOS) results were obtained during dissolution testing of Reclipsen (oral contraceptive) validation/method transfer lots and . The firm's investigation found that the validated method was flawed due to a physical-chemical interaction between the desogestrel (active ingredient) and the approved dissolution media. To minimize the impact of this interaction, several changes in sample handling and dissolution practices were implemented in March 2005. The original results were invalidated and the lots were released based on retest results. Additional changes to the method were identified and documented from July to December 2005. There is no assurance that the current method is able to consistently produce precise and accurate results. We are concerned with the number of modifications that you have made to the dissolution method in less than a year without conducting additional validation work. Please provide additional information demonstrating that the current dissolution method for Reclipsen tablets prevents the physical-chemical interaction between the desogestrel and the approved dissolution media.

In addition, lots and which were used to support process validation for Estazolam (treatment of insomnia) tablets failed blend uniformity testing. This validation was completed in July 2004. Your firm concluded that the most probable cause was sampling errors and determined that more data was needed to evaluate an increase in the size of the blend sample and a change to a different sample thief. Since then, three out of eight commercial lots also obtained OOS results for blend uniformity testing (lots , and). From November 2004 to September 2005, six lots were released based on acceptable unit dose testing results without completing the study and determining if increasing the sample size and changing the actual sample thief will produce acceptable blend uniformity testing results. We are concerned with your practice of releasing lots of Estazolam tablets that pass extended content uniformity testing but fail blend uniformity tests. We reviewed protocol , Estazolam tablets 2mg, Monitoring of Blend Uniformity Test, dated , and the final report on the study, dated . The results of this study do not appear to demonstrate that the increase of sample size provides a better correlation between the blend uniformity and content uniformity testing results.

Your FDA-483 response indicated that the failing blend uniformity results are due to sampling effects. It also stated that two of the validation batches, and , showed low blend uniformity results and that you had conducted extended content uniformity tests using compressed units from each failing batch in accordance with the October 2003 Draft Guidance for Industry for Powder Blends and Finished Dosage Units - Stratified In-Process Dosage Unit Sampling and Assessment. However, you did not provide evidence that you completed the accompanying assessment and investigation procedures recommended in this draft document.

Please note that the draft guidance referenced in your response provides an alternate method of using stratified sampling of dosage units to demonstrate adequacy of mix for powder blends. However, this procedure is not meant as a retest procedure for those lots that fail blend sample testing, nor does it recommend increasing the number of samples tested during finished product content uniformity to justify release of a lot that failed blend sample testing. It is intended as the in-process test to be used for all lots after you have determined that blend sampling does not provide an accurate evaluation of blend uniformity. If the stratified sampling method is selected as a more reliable test you should follow the sampling methods, sample sizes, and acceptance criteria recommended in the guidance. Whichever method is chosen as the in-process test the decision should be made based on sound scientific principles. Please provide the validation report of the new sample size for blend uniformity testing for Estazolam tablets which you indicated would be completed by March 31, 2006.

Neither this letter nor the observations noted on the Form FDA 483 are intended to be an all-inclusive list of the deficiencies that may exist at your facilities. It is your responsibility to ensure that your operations are in full compliance with all applicable requirements of the Act and the implementing regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these violations, and you should establish procedures whereby such violations do not recur. Failure to do so may result in regulatory action without further notice, including seizure and/or injunction.

We request that you reply in writing within 15 working days of receipt of this letter, stating the action that you will take to correct the noted violations and ensure that corrections will be put in place. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed.

Your reply should be sent to the Food & Drug Administration, San Juan District Office, 466 Fernandez Juncos Ave., San Juan, PR 00901-3223, to the Attention of Margarita Santiago, Compliance Officer.

Sincerely,

Maridalia Torres
Acting District Director
San Juan District